UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/887,194	06/22/2001	Kimberly F. Glassman	BB1449 US NA	9205

23906 7590 02/25/2004

E I DU PONT DE NEMOURS AND COMPANY
LEGAL PATENT RECORDS CENTER
BARLEY MILL PLAZA 25/1128
4417 LANCASTER PIKE
WILMINGTON, DE 19805

EXAMINER
LACOURCIERE, KAREN A

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 02/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/887,194	GLASSMAN ET AL.	
	Examiner	Art Unit	
	Karen A. Lacourciere	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *November 17, 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-45* is/are pending in the application.

4a) Of the above claim(s) *3-5,13-15 and 20-44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 6-12, 16-19, 45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

This application contains claims 3-5, 13-15, 20-44 and SEQ ID NO: 12 and 34 drawn to an invention nonelected without traverse in Paper No. 11. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 6-12, 16-19 and 45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 2, 6-12, 16-19 and 45 are indefinite due to the recitation "do not share sequence identity with any endogenous RNA in the host". It is unclear what degree of

difference is required to meet this claim limitation and how an RNA cannot share sequence identity with a host RNA at even one residue, for example.

Claims 1, 2, 6-12, 16-19 and 45 are indefinite because the claims recite RNA regions which are in proximity to the target mRNA or are 5' or 3' to the target mRNA, but it is unclear what the structure of this mRNA is. For example, it is unclear if a copy of the target mRNA is part of the recombinant structure or if the recombinant structure is integrated into the host to be expressed in proximity to the target mRNA which is expressed by the host. The claim language is so unclear that is impossible to determine what the structure of the claimed construct is or what the structure of construct used in the claimed methods is.

Claim 6 and claims dependent upon claim 6 are maintained as indefinite due to the recitation "a synthetic, non-naturally occurring RNA sequence". It is unclear what characteristics of an RNA would make it synthetic and non-naturally occurring, for example, the RNA of claim 6 is expressed by a vector in a cell, it is unclear how a portion of the RNA would be "synthetic" or "non-naturally occurring".

Claim 12 recites the limitation "the RNA" in line 9 of the claim. There is insufficient antecedent basis for this limitation in the claim, because claim 12 recites more than one RNA and it is unclear which RNA is being referred to.

Claim 16 and claims dependent upon claim 16 are maintained as indefinite due to the recitation "a synthetic, non-naturally occurring RNA sequence". It is unclear what characteristics of an RNA would make it "synthetic" and "non-naturally occurring".

Response to Arguments

Applicant's arguments filed November 17, 2003 have been fully considered but they are not persuasive. In response to the rejection of record under 35 USC 112, second paragraph of claims 6 and 12 (and claims dependent thereon) due to the recitaion "a synthetic, non-naturally occurring RNA sequence" Applicant argues that the term is defined on page 16 of the specification as "as artificial, non-consistent with what is normally found in nature" and, therefore, is clear and definite. This is not persuasive because the definition provided does not provide a definition that would provide clear metes and bounds to the skilled artisan. For example, each of the embodiments disclosed in the specification is consistent with nature in that it comprises naturally occurring nucleotides and a naturally occurring backbone. In what respect would an RNA be "a synthetic, non-naturally occurring RNA sequence", but also fit within the embodiments disclosed in the specification. It is unclear how and to what degree an RNA differs from that in nature to be encompassed in the term "a synthetic, non-naturally occurring RNA sequence".

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 8-10 and 18-20 are maintained as rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of reducing the expression of a target gene in a host cell in vitro (cell culture) or in a plant, does not

reasonably provide enablement for methods of reducing expression of a target RNA in a host or host cell in vivo (whole organism) in a vertebrate host. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Claims 8-10 and 18-20 are drawn broadly to methods of reducing the expression of a target mRNA in generally any host cell, in any setting, including in a vertebrate host cell in vivo (whole organism), using a double stranded RNA molecule comprising a region with homology to a target molecule or a vector expressing the double stranded RNA molecule, which encompasses gene therapy methods and dsRNA inhibition, as well as antisense methods (particularly given the broad meaning of "homology").

The specification provides examples wherein plant genes are inhibited using dsRNA and expressed dsRNA. The specification has not provided any examples wherein a dsRNA or a vector expressing a dsRNA is delivered to a vertebrate cell in vivo (whole organism) in a host organism.

At the time of the instant invention, and even to date, methods of inhibiting gene expression using nucleic acids in vivo(whole organism) are highly unpredictable, mainly due to issues of how to specifically deliver a nucleic acid molecule or vector to a target cell at a concentration effective to result in a desired effect, and, in the case of gene therapy, the determination of target cell specific vectors and promoters to achieve and maintain expression of the gene. Gene therapy methods (ie. nucleic acids expressed from a vector) are further hampered by unpredictable loss of expression (see for example Branch, Crooke, Anderson and Verma et al.). The specification states that the claimed methods differ from antisense methods by acting through a different, but undefined, mechanism. Despite the mechanism, the methods claimed require that an RNA, or vector expressing said RNA, be delivered specifically to a target cell in an organism in vivo(whole organism) at a concentration effective enough to inhibit the expression of a target gene. As such, although Branch, Agrawal(TIBTech), Verma et al. and Anderson discuss issues of delivery and expression in reference to antisense methods and gene therapy vectors expressing protein products, the same art recognized issues of enablement would apply to the instantly claimed methods. The specification provides guidance with respect to delivery of double stranded RNA molecules, or vectors expressing such, into plant cells, or into plant embryos, which can then develop into a whole plant, however, the specification does not provide any specific guidance that would enable one skilled in the art to overcome the art recognized unpredictability of specific delivery of nucleic acids (or vectors) to a target cell, or effective and sustained expression of a vector expressing such a nucleic acid in

any other organism besides a plant. The guidance provided for plants would not be expected to translate into generally any other organism because methods of delivering nucleic acids in plants are very different than those for other organisms, especially vertebrates, including mammals. For example, mammals, including humans, have demonstrated an immune response triggered by even small amounts of double stranded RNA that would preclude the use of double stranded RNA in vivo (whole organism).

To practice the methods claimed, over the full scope claimed, it would require undue trial and error experimentation for the skilled artisan. Such experimentation would include the determination of how to specifically deliver a double stranded RNA or a vector to a target cell at a concentration effective enough to inhibit the expression of a target gene, the determination of an appropriate vector and enhancer-promoter combination for each target cell type "the search for such combinations is a case of trial and error for a given type of cell."(see Verma, for example p 240, columns 2 and 3), how to overcome the effects of dsRNA induced immune response.

Therefore, based on the breadth of the claims, the nature of the invention, the state of the art, the high level of unpredictability in the art, the lack of specific guidance by the inventor (beyond plants), the lack of working examples (beyond plants), and the quantity of experimentation that would be required, it would require undue experimentation, beyond what is taught in the specification, to practice the methods as claimed, over the full scope claimed.

Response to Arguments

Applicant's arguments filed November 17, 2003 have been fully considered but they are not persuasive. In response to the rejection of record of claims 8-10 and 18-20 under 35 USC 112, first paragraph, as not being enabling, Applicant argues that the amendment to recite an invertebrate host is sufficient to overcome the rejection of record. This is not found to be persuasive because this amendment does not change the scope of the claims to exclude methods in an invertebrate in vivo in a whole organism. A host invertebrate would encompass a whole organism and would be subject to the same undue experimentation as discussed in the rejection of record.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in-
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

Claims 1, 2, 6-12 and 16-19 are maintained as rejected under 35 U.S.C. 102(b) as being anticipated by Thompson (US Patent No. 5,902,880).

Thompson discloses and claims RNA molecules wherein the molecule comprises a region of homology to a target RNA (for example, an antisense molecule) and further comprises complementary RNA regions that hybridize to form a hairpin, wherein the complementary regions are unrelated to the target molecule. The complementary regions disclosed by Thompson do not comprise plant viral RNA. Thompson further discloses vectors that express these RNA molecules and discloses transforming host cells with the vector or RNA and inhibiting the expression of a target gene in the host cell.

Therefore, Thompson anticipates claims 1, 2, 6-12 and 16-19.

Claims 1, 2, 6-12 and 16-19 are maintained rejected under 35 U.S.C. 102(e) as being anticipated by Thompson (US Patent No. 6,146,886).

Thompson discloses and claims RNA molecules wherein the molecule comprises a region of homology to a target RNA (for example, an antisense molecule) and further comprises complementary RNA regions that hybridize to form a hairpin, wherein the complementary regions are unrelated to the target molecule. The complementary regions disclosed by Thompson do not comprise plant viral RNA. Thompson further discloses vectors that express these RNA molecules and discloses transforming host cells with the vector or RNA and inhibiting the expression of a target gene in the host cell.

Response to Arguments

Applicant's arguments filed 11-17-2003 have been fully considered but they are not persuasive. In response to the rejection of record of claims 1, 2, 6-12 and 16-19 under 35 USC 102(b) as anticipated by Thompson (US Patent No. 5,902,880) Applicant argues that Thompson '880 is concerned with the expression of therapeutic RNA's so that they accumulate intracellularly, whereas the present application is concerned with reducing expression of a target RNA in an invertebrate host and, therefore, Thompson does not anticipate all the limitation of the instant invention.

This has not been found to be persuasive because Thompson '880 discloses RNA's with all of the limitations of the claimed RNA molecules, and the molecules of Thompson '880 are molecules that include regions of antisense that bind to a target mRNA in an invertebrate host and reduce the expression of the target RNA and, therefore, meet all of the limitations of the claimed invention.

In response to the rejection of record of claims 1, 2, 6-12 and 16-19 under 35 USC 102(e) as being anticipated by Thompson (US Patent No. 6,146,886), Applicant argues that Thompson '886 is concerned with the expression of therapeutic RNA's so that they accumulate intracellularly, whereas the present application is concerned with reducing expression of a target RNA in an invertebrate host and, therefore, Thompson does not anticipate all the limitation of the instant invention.

This has not been found to be persuasive because Thompson '886 discloses RNA's with all of the limitations of the claimed RNA molecules, and the molecules of Thompson '886 are molecules that include regions of antisense that bind to a target mRNA in an invertebrate host and reduce the expression of the target RNA and, therefore, meet all of the limitations of the claimed invention.

Conclusion

Any rejection of record not repeated herein is considered to be withdrawn.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Lacourciere whose telephone number is (703) 308-7523. The examiner can normally be reached on Monday-Thursday 6:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 305-1935 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Karen A. Lacourciere
February 23, 2004

KAREN A. LACOURCIERE, PH.D
PRIMARY EXAMINER